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UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001

September 29, 1992

(A)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

8EHQ-92-12143
INIT
8892001038 1

Document Processing Center (TS-790)
Room L-100
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

Re: CAP Agreement Identification No. 8ECAP-0110

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith lists the following report pursuant to the terms of the TSCA §8(e) Compliance Audit Program and Union Carbide's CAP Agreement dated August 14, 1991 (8ECAP-0110). The report describes acute inhalatin toxicity, human response to low concentrations and sensitization studies with methyl isocyanate (CASRN 624-83-9).

"Methyl Isocyanate: Acute inhalation toxicity, human response to low concentrations, guinea pig sensitization, and cross sensitization to other isocyanates", Chemical Hygiene Fellowship (Carnegie-Mellon University), Special Report 33-19, March 5, 1970.

This information was previously submitted to the Agency in the following manner:

UCC letter of 12/17/84 to TSCA 8(e) Office.

An additional copy of this study is attached.

A complete summary of this report is attached.

12/1/94

33-19

Previous TSCA Section 8(e) or "FYI" Submission(s) related to this substance are:

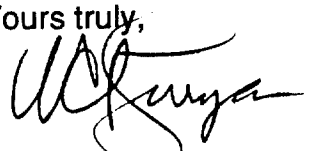
8EHQ-0381-0392

Previous PMN submissions related to this substance are: (None)

This information is submitted in light of EPA's current guidance. Union Carbide does not necessarily agree that this information reasonably supports the conclusion that the subject chemical presents a substantial risk of injury to health or the environment.

In the attached report the term "CONFIDENTIAL" may appear. This precautionary statement was for internal use at the time of issuance of the report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Yours truly,



William C. Kuryla, Ph.D.
Associate Director
Product Safety
(203/794-5230)

WCK/cr
Attachment (3 copies of cover letter, summary, and report)

SUMMARY

Confidential
Special Report 33-19
8 Pages

R: 3-5-70

Chemical Hygiene Fellowship
MELLON INSTITUTE
Carnegie-Mellon University

Methyl Isocyanate

Acute inhalation toxicity, human response to low concentrations, guinea pig sensitization, and cross sensitization to other isocyanates

Editor: H. F. Smyth, Jr., Contributors: E. R. Kinkead, U. C. Pozzani, L. J. Sullivan
For: UNION CARBIDE CORPORATION, Chemicals and Plastics Operations Division

Summary

Hitherto unreported experimental data on the toxicity of methyl isocyanate confirm that it is highly toxic by inhalation, irritant to humans at very low vapor concentrations, and a potent skin sensitizer. Guinea pigs sensitized to methyl isocyanate were also sensitive, but to a lesser degree, to some other isocyanates. Such sensitization is not a rapidly transient condition. In a group of guinea pigs sensitized to another isocyanate (TDI), response to a challenge dose fourteen weeks later was as intense as response to a challenge at completion of the experimental sensitization.

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Introduction

In May 1966, the Fellowship presented a paper on methyl isocyanate before the American Industrial Hygiene Association entitled "Animal and Human Response to Methyl Isocyanate," by U. C. Pozzani and E. R. Kinkead.

Somewhat earlier a German publication (Kimmerle and Eben, 1964) covered much the same ground, and indeed went further in that several species of rodents were used and one inhalation test was repeated on five successive days. It was concluded that there is not sufficient new data in the Fellowship's work to justify journal publication.

The only other information on the toxicity of methyl isocyanate which was found in the literature was range-finding data published by the Fellowship (Smyth, et al., 1969).

Material

All of the material studied was obtained from Eastman Organic Chemicals, Rochester, New York. Nine containers of Catalog Number 6699, 25 or 100 grams each, were purchased during the 36-month period ending in the spring of 1966.

Methyl isocyanate is a colorless liquid with a piercing odor. It boils at 39.1°C. Its vapor pressure at room temperature is approximately 430 mm., hence saturated vapors are 570,000 ppm. by volume. Its molecular weight is 57.05. One ppm. is equivalent to 0.00233 mg./liter of air, one mg./liter to 428.57 ppm.

Analytical

A gas chromatographic method was standardized for analytically determining the concentrations to which animals were exposed. The conditions are listed below.

Instrument:	Barber Coleman Series 5000 with hydrogen flame ionization detector
Column:	Glass, 230 x 0.6 cm.
Solid Support:	Gas Chrom Q 80/100 mesh
Stationary Phase:	30% Silicone Oil 550
Column Temperature:	50°C.
Carrier Gas:	Helium at 170 ml./minute

This method was found to have a sensitivity of 0.1 ppm. with 80 to 90% accuracy, using 0.1 to 10 ml. air samples, within the range used for inhalation exposures.

Range-Finding Toxicity Data

Range-finding toxicity data appeared in M. I. Special Report 26-75 in 1963, and has been recently published (Smyth, et al., 1969). It may be outlined as follows.

Rat LD50 by stomach intubation - 0.071 gm./kg. as a 10% solution in Deobase.
Rabbit LD50 by skin penetration - 0.22 ml./kg. undiluted.
Rat 4-hour inhalation of metered (nominal) concentrations -
62.5 ppm. killed 6 of 6
31.2 ppm. killed 0 of 6
2 mg./liter (857 ppm.) killed 6 of 6 after 1 hour.
Uncovered skin irritation, rabbit - severe necrosis, Grade 6.
Eye injury, rabbit - severe necrosis, Grade 10.
Sensitization, guinea pig dermal - 16 of 16 sensitized.
DOT Class B poison by virtue of inhalation and skin toxicity.

Inhalation Toxicity

Groups of six male Harlan Wistar albino rats were exposed to flowing streams of metered concentrations of methyl isocyanate vapors for periods ranging from 7.5 minutes to 4 hours, and observed for 14 days for symptoms and survival. Guinea pigs were exposed only for 4-hour periods.

The behavior of the animals in the exposure chamber indicated eye, nose and lung irritation proportional to the concentrations. Even as low a concentration as 8.9 ppm. caused gasping and labored breathing, but at 4.47 ppm. there was only transient eye and nose irritation in the rats, not evident after four hours exposure, and respiration was normal. Symptoms and gross pathology after the exposures were primarily explainable on the basis of lung irritation, with death resulting from lung edema.

The method for analysis of vapor concentration was not fully developed until after exposures were completed. Analysis of a range of metered concentrations showed the true concentrations to average 38.31% of the metering indications. The data in this section have been corrected for this value and represent analytically verified concentrations.

Species	Inhalation time, minutes	LC50 in ppm. with 95% Confidence limits	C T value, ppm. - minutes
Rat	240	17.5	4200
	120	27.4 (20.7 - 36.3)	3288
	60	41.3 (23.6 - 71.0)	2478
	30	76.6 (61.2 - 95.9)	2298
	15	216 (162 - 286)	3240
	7.5	541 (241 - 1216)	4058
Guinea Pigs	240	10.6	2544

The last column indicates an essentially constant product of concentration and inhalation time for fatality, within the limits tested. This result is to be expected for a material which is a severe lung irritant.

Guinea pigs appear to be somewhat more susceptible than rats, but this is not certain since no confidence limits can be calculated for the 240 minute exposures.

Human Response to Low Concentrations

Eight human volunteers were exposed for one minute in a ceramic lined chamber to an analytically verified concentration of 1.75 ppm. (0.004 mg./L.) methyl isocyanate. They reported the following responses:

Odor	0 subjects
Eye irritation	8 subjects
Tearing	7 subjects
Nose irritation	3 subjects
Throat irritation	3 subjects

All effects disappeared within 10 minutes, except that one young woman reported a sensation of having something in her eye for 45 minutes.

Six of the same persons were exposed for 10 minutes to 0.5 ppm. (0.0012 mg./L.). Eye irritation was evident earliest, and was experienced by all. Tearing, nose and throat irritation were less evident. One person perceived an odor. Individual reports of response are summarized below:

Minutes in exposure	Number of persons reporting:- Eye Irrit.	Tearing	Nose Irrit.	Throat Irrit.	Odor
1	0	0	0	0	0
2	3	0	0	1	0
3	3	1	3	3	1
5	5	5	5	3	0
7	5	5	5	3	0
9	5	5	4	2	0
10	6	5	4	2	0

Eye irritation and tearing did not decrease during the 10-minute exposure period, but apparently there was some slight decrease in perception of nose and throat irritation.

Allergic Sensitization

Occupational experience with diisocyanates is marked by a high incidence of respiratory tract sensitizations and a low incidence of dermal sensitizations. Unfortunately there is no generally accepted animal test for detecting a specific potential for respiratory tract sensitization. Since the immunological mechanisms for sensitization in the two areas appear to be closely similar, reliance on the well established Landsteiner guinea pig test for dermal sensitizing potential is acceptable for predicting respiratory tract sensitizing potential.

Because of the well-known high sensitizing potential of diisocyanates, and the primary irritation of methyl isocyanate, it was tested at one-tenth the concentration we have found appropriate for testing the usual industrial chemical. Adult male albino guinea pigs were given intracutaneous injections of a 0.01% solution in peanut oil in the upper right scapular area. The initial injection was 0.05 ml. Seven 0.1 ml. injections followed at the rate of three a week, using a different site for each injection. After three weeks with no injections, sensitization is complete in those pigs which are sensitized at all. Sensitization is detected by the wheal elicited by a challenge dose of 0.05 ml. injected intracutaneously in the clipped skin of the lower right scapular area. Its degree is evaluated by estimating the area, redness and elevation of the wheal, using a numerical system in which negative response scores $\leq$ 25 and definite but not extreme response scores $\leq$ 100.

Sixteen of 16 guinea pigs gave a positive sensitization response to methyl isocyanate, scoring 234 at 24 hours after the challenge injection and 358 at 48 hours. This is as high a sensitizing potential as any chemical we have ever tested.

Cross Sensitization

The usual sensitizing chemical handled in industry requires a series of doses to guinea pigs to cause sensitization. Methyl isocyanate is so potent a sensitizer that one dose is enough. Each of 3 guinea pigs was given a single intradermal injection of 0.1 ml. of 0.01% methyl isocyanate in peanut oil. Forty-eight days later they were given an intradermal challenge of 0.05 ml. Responses scored 49 to 99 twenty-four hours later.

Report 26-75 on range-finding tests stated that the guinea pigs sensitized to methyl isocyanate did not react to a challenge injection of toluene diisocyanate, concluding that cross sensitization would not be an industrial problem. However, this work was repeated with different results. A group of guinea pigs was sensitized to methyl isocyanate and another group to toluene diisocyanate. The pigs in each group were given two challenge doses, on one side the compound used to sensitize them, and on the other side the other isocyanate. The results are shown below.

	Response to challenge of			
	Methyl isocyanate		Toluene diisocyanate	
Sensitizer	number	score	number	score
Toluene diisocyanate	10 of 16	37	15 of 16	379
Methyl isocyanate	20 of 20	255	7 of 20	40

Although the cross sensitization reactions are light, they do show that a degree of cross sensitization takes place.

Cross sensitization was further tested on the same two groups of guinea pigs using other isocyanates which were then in the laboratory. The following showed some degree of cross sensitization reaction on one or the other group of pigs.

Hexamethylene disocyanate (HMDI)
Bis(2-isocyanatoethyl) carbonate (CDI-X)
Bis(2-isocyanatoethyl) fumarate (FDI-X)

Three other isocyanates did not show cross sensation reactions. This result is less conclusive because there is a possibility that the frequent testing of the same animals had so depleted their store of antibodies that a wheal could not be formed. The doubtful compounds were:

Phenyl isocyanate (PHI)
Bis(2-isocyanatoethyl)-3,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylate (HEDI)
Bis(2-isocyanatoethyl)-5-cyclohexene-2,3-dicarboxylate (CEDI)

None of the cross sensitization reactions was as severe as the homologous reactions to the isocyanate used to sensitize a group of guinea pigs. Nevertheless, response was definite. This is in accord with the general belief in industry that a man sensitized to one isocyanate cannot work with any other isocyanate.

Topical Sensitization

A single large application of methyl isocyanate to the skin was found to sensitize guinea pigs. One drop (about 0.06 ml.) of undiluted methyl isocyanate was applied to the sacral area of each of nine animals. Three weeks later an intradermal challenge elicited a reaction on all 9 animals, having an average score of 109.

It appears that methyl isocyanate is very rapidly bound to the skin or penetrates into its outer layers. Immediately after the topical sensitizing application described above, the contacted area on three of the pigs was washed with soap and water, and on three others it was given a 5-second air blast, then washed. The reactions to challenge did not indicate any success in these efforts to remove the isocyanate.

Inhalation Sensitization

An attempt was made to produce respiratory sensitization with methyl isocyanate, although such attempts with known respiratory sensitizers are seldom successful. Nineteen guinea pigs were exposed to a measured concentration of one ppm. for two hours a day three times a week for three weeks. The total absorption of methyl isocyanate during the 9 inhalations was calculated to approximate that used for intradermal sensitization.

After a three-week incubation interval, 7 of the animals were exposed for two hours to one ppm. of methyl isocyanate, and another 7 to five ppm. No symptoms suggesting tracheal edema or other evidence of respiratory allergic response were seen.

The following day all of the 19 guinea pigs were given an intradermal challenge dose of isocyanate. Eleven of the 14 which had received the inhalation challenge responded, with an average score of 95. The 5 not earlier challenged all responded, with an average score of 107.

Closely similar results were obtained with toluene diisocyanate.

It is possible that it was exposure of skin to isocyanate vapor during the 9 sensitizing inhalations which resulted in the dermal sensitization detected by responses to the intradermal challenge. This seems unlikely, in view of the very low concentration (in milligrams per square centimeter) which skin exposure to 1 ppm. methyl isocyanate (0.00233 mg./liter) could produce, but the conditions of the exposure of the entire animal do not exclude the possibility.

Ineffective Dosage

Report 29-78 gives observations on toluene diisocyanate pertinent to this subheading, although we have no data on methyl isocyanate. Groups of guinea pigs were sensitized with an intradermal series of one 0.05 ml. injection and seven 0.1 ml. injections, with a 0.05 ml. challenge injection after a three-week interval using a different TDI concentration for each group.

In the group which received this treatment with a 0.01% solution of toluene diisocyanate in peanut oil, 13 of 15 responded with a reaction scoring 224 at 24 hours. In the group which received a 0.003% solution in peanut oil, none of 17 pigs responded.

When a specific sensitizing schedule is followed, there is a dosage below which sensitization does not result. It is possible that a longer schedule of intradermal injection would result in sensitization from the lower concentration.

Duration of Sensitization

Pertinent evidence on the duration of sensitization has not previously been reported. Guinea pigs were sensitized to bis(2-isocyanatoethyl) fumarate by an intracutaneous injection series. Some were challenged after the usual 3-week interval, some after a 14-week interval. There was no quantitative difference in the reactions of the two groups. It appears that there is no rapid decrease in experimental dermal sensitization to an isocyanate.

Discussion

The conclusions of this report do not conflict with those of Kimmerle and Eben (1964), although there are numerical differences in quantitative results. They exposed groups of 20 rats to measured concentrations of methyl isocyanate vapors produced by evaporation of solutions in methylene chloride or dimethyl sulfoxide.

In a two-hour exposure their LC50 was 0.049 mg./liter (21 ppm.), closely comparable to our figure of 27.4 ppm. However, their results at lower concentrations indicate a greater toxicity than do ours. Their four-hour LC50 was approximately 0.012 mg./liter (5.1 ppm.) while ours was 17.5 ppm. At 0.005 mg./liter (2.2 ppm.) for two hours, or at 0.0027 mg./liter (1.16 ppm.) for four hours on 5 successive days no injury to the rats resulted.

Kimmerle and Eben (1964), on the other hand found a somewhat lower degree of human sensory response than we found. In one to five-minute exposure of four humans to 0.4 ppm. they found no odor or irritation while we found quite definite eye, nose and throat irritation among six subjects at 0.5 ppm. for ten minutes, but no odor.

At 2 ppm. they found tears and irritation but no odor, quite comparable to our results at 1.75 ppm. They reported 21 ppm. to be unbearable, while we did not expose humans to such a high concentration.

Kimmerle and Eben (1964), reported severe irritation with necrosis from covered or uncovered applications to the rabbit ear, quite similar to our Grade 6 finding from uncovered application to the rabbit belly. They did not report tests of sensitization potential.

Henry F. Smyth, Jr., Ph.D.
Advisory Fellow

Approved:

Charles P. Carpenter, Ph.D.
Administrative Fellow

Acknowledgments:

Experimental Design and Coordination	U. C. Pozzani, M.S. Senior Fellow
Inhalation and Sensitization Studies	E. R. Kinkead, B.S. Junior Fellow
Analytical Method	L. J. Sullivan, M.S. Senior Fellow

Typed: March 6, 1970 - md

References

Kimmerle, G. and A. Eben (1964). Zur Toxicität von Methylisocyanat und dessen quantitativer Bestimmung in der Luft; Archiv. fur Toxikologie, 20, 235-241.

Smyth, H. F., Jr., C. P. Carpenter, C. S. Weil, U. C. Pozzani, J. A. Striegel and J. S. Nycum (1969). Range-finding toxicity Data: List VII; Amer. Industrial Hygiene Assoc. J., 30, 470-476.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

FEB 27 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and **refer to the reverse side of this page for "EPA Information Requests"** .

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12143A

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0992 -12143 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Union Carbide Corporation

SUB. DATE: 09/29/92 10/07/92 CSRAD DATE: 12/01/94

CHEMICAL NAME:

CAS#
624-83-9

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
(0210)	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
(0228)	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
(0243)	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

Atox/Sen

TRIAGE DATE:

NON-CBI INVENTORY:
(YES)
CAS SR
NO
IN TRAINING

ONGOING REVIEW:
YES (DROP/REFER)
NO (CONTINUE)
BLIP

SPECIES:
GP
HMN
RAT

TOXICOLOGICAL CONCERN:
RBT LOW
(MED)
(HIGH)

USE:

PRODUCTION:

8EHQ-0381-0392

-CPSS- 0301960919

0 0 0 0 0 0 0 0 0 0 0

> <ID NUMBER>
8(E)-12143A

> <TOX CONCERN>
H/M

> <COMMENT>
METHYL ISOCYANATE: ACUTE INHALATION TOXICITY IN RATS AND GUINEA PIGS IS OF HIGH CONCERN. SINGLE WHOLE-BODY EXPOSURES BY INHALATION WERE ASSOCIATED WITH EXPOSURE DURATION LC50 VALUES IN GROUPS OF 6 EACH MALE HARLAN WISTAR ALBINO RATS AS FOLLOWS: 17.5 PPM (240 MIN), 27.4 PPM (120 MIN), 41.3 PPM (60 MIN), 76.6 PPM (30 MIN), 216 PPM (15 MIN), 541 PPM (7.5 MIN). SINGLE 240-MINUTE WHOLE-BODY EXPOSURES TO GUINEA PIGS WERE ASSOCIATED WITH AN LC50 OF 10.6 PPM. SIGNS OF TOXICITY INCLUDED DOSE-DEPENDENT EYE, NOSE AND LUNG IRRITATION AS INDICATED BY GASPING AND LABORED BREATHING. LUNG EDEMA WAS FOUND ON NECROPSY OF DECEDENT ANIMALS.

METHYL ISOCYANATE: SINGLE 60 SECOND WHOLE-BODY EXPOSURES TO HUMANS OF A CONCENTRATION OF 1.75 PPM (0.004 MG/L) IN 8 HUMAN SUBJECTS WERE ASSOCIATED WITH EYE IRRITATION (8/8), TEARING (7/8), NOSE IRRITATION (3/8) AND THROAT IRRITATION (3/8). ALL BUT ONE WOMAN WITH A 45 MINUTE SENSATION OF SOMETHING IN HER EYE WERE CLEAR OF SYMPTOMS WITHIN 10 MINUTES OF EXPOSURE. SINGLE 10-MINUTE EXPOSURES OF 0.5 PPM (0.0012 MG/L) TO 6 HUMAN VOLUNTEERS WERE ASSOCIATED WITH EYE IRRITATION (6/10), NOSE IRRITATION (5/10), THROAT IRRITATION (3/10), TEARING (5/10) AND SENSATION OF ODOR (1/10).

METHYL ISOCYANATE: DERMAL SENSITIZATION IN MALE ALBINO GUINEA PIGS IS OF HIGH CONCERN. FOLLOWING INDUCTION WITH A SINGLE 0.05 ML INTRACUTANEOUS INJECTION OF A 0.01% SOLUTION AND 7 SUBSEQUENT TRIWEEKLY 0.1 ML INJECTIONS AT DISTINCT SITES ON THE SKIN OF 16 GUINEA PIGS, CHALLENGE AFTER THREE WEEKS' RESTING PHASE WITH A SINGLE 0.05 ML APPLICATION OF 0.01 SOLUTION TO A NAIVE SITE WAS ASSOCIATED WITH RESPONSE IN 16/16 ANIMALS. RESPONSE CONSISTED OF REDNESS AND ELEVATION OF A WHEAL PRODUCED AT THE SITE OF INJECTION. GIVEN INDUCTION WITH A SINGLE INJECTION OF 0.1 ML OF A 0.01% SOLUTION, 3 GUINEA PIGS CHALLENGED 48 DAYS LATER WITH 0.05 ML RESPONDED WITH IRRITATION SCORES OF 49 TO 99 AT 24-HOUR EVALUATION.

METHYL ISOCYANATE: DERMAL SENSITIZATION IN MALE ALBINO GUINEA PIGS IS OF HIGH CONCERN. A SINGLE DROP (0.06 ML) OF UNDILUTED SOLUTION APPLIED TO THE SKIN OF 9 GUINEA PIGS PRODUCED RESPONSE IN 9/9 ANIMALS UPON INTRADERMAL CHALLENGE 3 WEEKS LATER. ATTEMPTS TO REMOVE THE TEST MATERIAL FROM THE APPLICATION SITES FOLLOWING INDUCTION DID NOT ALTER THE SENSITIZATION RESPONSE UPON CHALLENGE IN 6/6 GUINEA PIGS.

METHYL ISOCYANATE: CROSS SENSITIZATION IN MALE ALBINO GUINEA PIGS IS OF MEDIUM CONCERN. GROUPS OF 16 AND 20 GUINEA PIGS WERE SENSITIZED TO TOLUENE DIISOCYANATE AND METHYL ISOCYANATE

RESPECTIVELY. RESPONSE WHEN CHALLENGED WITH THE HOMOLOGOUS ISOCYANATE WAS 15/16 AND 20/20 FOR THE TOLUENE AND METHYL ISOCYANATE SENSITIZED ANIMALS, WHILE CROSS SENSITIZATION TO THE OTHER ISOCYANATE WAS 10/16 AND 7/20 RESPECTIVELY. THESE SAME GROUPS OF GUINEA PIGS WERE REPORTED TO HAVE SOME DEGREE OF CROSS SENSITIZATION TO HEXAMETHYLENE DIISOCYANATE, BIS(2-ISOCYANATOETHYL) CARBONATE, AND BIS(2-ISOCYANATOETHYL) FUMARATE, WHILE NO CROSS SENSITIZATION WAS OBSERVED WITH PHENYL ISOCYANATE, BIS(2-ISOCYANATOETHYL)-3,4,5,6,7,7- HEXACHLORO-5-NORBORNENE-2,3-DICARBOXYLATE, AND BIS(2-ISOCYANATOETHYL)-5- CYCLOHEXENE-2,3-DICARBOXYLATE.

METHYL ISOCYANATE: PULMONARY SENSITIZATION IN GUINEA PIGS IS OF HIGH CONCERN. FOLLOWING INDUCTION WITH 2-HOUR DAILY EXPOSURES OF 1 PPM 3 TIMES PER WEEK FOR 3 WEEKS TO NINETEEN GUINEA PIGS, CHALLENGE TO GROUPS OF 7 EACH GUINEA PIGS AFTER THREE-WEEK INCUBATION WITH 1 PPM OR 5 PPM WERE ASSOCIATED WITH NO RESPONSE IN ANY ANIMAL. SECOND CHALLENGE TO THESE 14 ANIMALS AND FIRST CHALLENGE TO THE REMAINING 5 SENSITIZED ANIMALS WITH INTRADERMAL ISOCYANATE (CONCENTRATION UNSPECIFIED) PRODUCED RESPONSE IN 11/14 AND 5/5 ANIMALS RESPECTIVELY.

TOLUENE DIISOCYANATE: PULMONARY SENSITIZATION IN GUINEA PIGS IS OF HIGH CONCERN. FOLLOWING INDUCTION WITH 2-HOUR DAILY EXPOSURES OF 1 PPM 3 TIMES PER WEEK FOR 3 WEEKS TO NINETEEN GUINEA PIGS, CHALLENGE TO GROUPS OF 7 EACH GUINEA PIGS AFTER THREE-WEEK INCUBATION WITH 1 PPM OR 5 PPM WERE ASSOCIATED WITH NO RESPONSE IN ANY ANIMAL. SECOND CHALLENGE TO THESE 14 ANIMALS AND FIRST CHALLENGE TO THE REMAINING 5 SENSITIZED ANIMALS WITH INTRADERMAL ISOCYANATE (CONCENTRATION UNSPECIFIED) PRODUCED RESPONSE IN MOST ANIMALS (NUMBERS UNSPECIFIED) OF BOTH GROUPS.

TOLUENE DIISOCYANATE: DERMAL SENSITIZATION IN MALE ALBINO GUINEA PIGS IS OF HIGH CONCERN. FOLLOWING INDUCTION WITH A SINGLE 0.5 ML INTRACUTANEOUS INJECTION OF 0.01% SOLUTION AND 7 SUBSEQUENT TRIWEEKLY 0.1 ML INJECTIONS AT DISTINCT SITES ON THE SKIN OF 16 GUINEA PIGS, CHALLENGE AFTER THREE WEEKS' RESTING PHASE WITH A SINGLE 0.05 ML INTRACUTANEOUS INJECTION OF 0.01% SOLUTION TO A NAIVE SITE WAS ASSOCIATED WITH RESPONSE IN 13/15 ANIMALS. CHALLENGE WITH A 0.003% INJECTION PRODUCED NO RESPONSE IN 17 ANIMALS.

BIS(2-ISOCYANATOETHYL) FUMARATE: NO LEVEL OF CONCERN IS ASSIGNED DERMAL SENSITIZATION IN GUINEA PIGS DUE TO LACK OF SPECIFIC RESPONSE DATA. FOLLOWING INDUCTION WITH A SERIES OF INTRACUTANEOUS INJECTIONS, CHALLENGE AFTER 3-WEEK AND 14-WEEK RESTING PHASES "PRODUCED NO QUANTITATIVE DIFFERENCE IN THE REACTIONS OF THE TWO GROUPS".

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EQMS Ratings on 8(E) Submissions--CAP Set 48--July 28, 1995

8E Number and Chemical Name	Rank	Reason or Brief Description
-11924 Pentaerythritol triacrylate, PETA, CAS 3524-68-3	Med	In 1965 a large chemical manufacturer screened its printing-ink mixtures for irritancy/sensitivity by submitting three proprietary formulations to an outside university consultant dermatologist. One of the mixtures containing PETA consistently induced reactions typical of sensitization, under occlusive conditions at 1 % concentration.
-12044 Hexahydro-1,3,5-tris 2(hydroxyethyl) triazine, CAS 4719-04-4	High	1977 correspondence from a European chemical company identified the subject chemical as a concentration-dependent sensitizer, despite an earlier report from the original manufacturer that it was not. Appended are handwritten animal results. The latter contains anecdotal human reports of sensitization in a cutting fluid use. At the time of correspondence the chemical was to be a component of textile spin finishes at 0.15% concentration or below.
-12143 Methyl isocyanate, TDI	Med	A 1970 report submitted in 1992, that 8 volunteers exposed for one minute to 1.75 ppm showed transient irritation effects. Six of them were also exposed ten minutes to 0.5 ppm and all showed eye irritation,and 4 showed nose irritation. The report does not indicate which exposure occurred first.

Triage of 8(e) Submissions

Date sent to triage: MAR 0 8 1995

NON-CAP (CAP)

Submission number: 12143A

TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

(ATOX) SBTOX (SEN) w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX (ERI) RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: 0 (1) 2 **pages** 1,2 **pages** 1-3

Notes:

Contractor reviewer : LPS **Date:** 1/25/95